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Penicillin Use in Meningococcal Disease Management: Active Bacterial Core Surveillance Sites, 2009

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In 2009, in the Active Bacterial Core surveillance sites, penicillin was not commonly used to treat meningococcal disease. This is likely because of inconsistent availability of antimicrobial susceptibility testing and ease of use of third-generation cephalosporins. Consideration of current practices may inform future meningococcal disease management guidelines.

Keywords. antimicrobial resistance; meningitis; meningococcal disease; *Neisseria meningitidis*.

Meningococcal disease is a severe infection caused by the bacterium *Neisseria meningitidis*, which causes death or permanent disability in 1 of every 4 patients. Penicillin has historically been used for treatment of laboratory-confirmed meningococcal infections, and it remains a treatment of choice in both adult and pediatric treatment guidelines [1]. Vancomycin plus a broad-spectrum cephalosporin is recommended for empiric treatment of bacterial meningitis; when microbiologic diagnosis of *N meningitidis* is confirmed, penicillin is recommended, preferably with evidence of full susceptibility on antimicrobial susceptibility testing (AST) [2, 3].

We report the findings of an expanded medical record review project conducted in the Active Bacterial Core surveillance (ABCs) sites (1) to estimate the frequency of penicillin use to treat meningococcal disease and (2) to determine availability

of AST and its use in guiding treatment, as recommended by current adult and pediatric guidelines. Understanding current practices of healthcare providers in prescribing penicillin for treatment of meningococcal disease and the availability of AST are important to characterize the clinical and public health significance of any increased penicillin nonsusceptibility in *N meningitidis*, and these steps may help inform treatment recommendations.

METHODS

A retrospective expanded medical record review was conducted for *N meningitidis* cases reported to ABCs in 2009. Active Bacterial Core surveillance is an active, population- and laboratory-based surveillance system that is supported by the Centers for Disease Control and Prevention (CDC) as part of its Emerging Infections Program Network [4]. The ABCs sites that participated in the expanded medical record review included California (3 San Francisco Bay area counties), Colorado (5 Denver area counties), Connecticut, Georgia's Atlanta Metropolitan Statistical Area, Maryland, Minnesota, New Mexico, Oregon, New York (15 Rochester and Albany area counties), and Tennessee (11 urban counties). The population under surveillance in these sites in 2009 was 36 748 349, representing 12.0% of the US population.

A case was defined as isolation of *N meningitidis* from a normally sterile site (eg, blood or cerebrospinal fluid) in a resident of a surveillance area. Syndrome was defined as the clinical diagnosis reported in the medical record (meningitis, pneumonia, or bacteremia).

The standard ABCs case-report form collects demographics, clinical syndrome, underlying conditions, serogroup, and outcome data abstracted from medical records. A 1-page, expanded form was used to collect the following: all antibiotics prescribed within the first 10 days of hospitalization; clinical tests and their results; AST availability, methods, and results; intensive care unit (ICU) admission; consultation with an infectious disease specialist; intubation; and concurrent infections.

Antimicrobial susceptibility testing was performed at the CDC using Etest antibiotic gradient strips. Mueller Hinton agar with 5% sheep blood (BD, Franklin Lakes, NJ) was used. Inoculum plating and strip application were carried out in accordance with the manufacturer's instruction, using an automatic turntable and a multiple strip dispenser (AB Biodisk). Antibiotic concentrations ranged from 0.016 to 256 µg/mL for penicillin. Currently, there are no standards for AST of meningococci approved by the Clinical Laboratory Standards Institute (CLSI). Etest minimum inhibitory concentrations (MICs) were interpreted by rounding up the half-dilution (if applicable) to

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the next standard broth microdilution 2-fold dilution before applying CLSI MIC breakpoints, as recommended by the manufacturer [5].

Statistical analysis was performed in SAS version 9.3 (SAS Institute, Inc., Cary, NC). Differences between proportions were tested using Pearson's χ^2 test or Fisher's exact test. Differences between means were tested using Student's *t* test.

RESULTS

In 2009, 123 cases of *N meningitidis* were reported by participating ABCs sites; of these, 122 had a medical record available for review. Cases had a median age of 24.5 years (range, 42 days–95 years), 64 cases (53%) were female, 83 cases (68%) were white, and 10 cases (8%) were Hispanic. No underlying conditions were present in 54 cases (44%). The most frequent underlying conditions or risk factors reported in adults were current smoking (*n* = 16, 21%) and diabetes (*n* = 14, 18%). The most frequently reported underlying conditions in pediatric cases were obesity (*n* = 2, 5%) and prematurity (*n* = 2, 5%). *Neisseria meningitidis* was isolated from blood in 96 cases (79%) and from cerebrospinal fluid in 34 cases (28%). Meningitis was the most common clinical syndrome (*n* = 52, 43%), followed by bacteremia (*n* = 36, 30%) and bacteremic pneumonia (*n* = 18, 15%).

An infectious disease specialist was consulted in 84 cases (69%), but there was no significant difference in treatment based on this consultation. Of 57 cases (47%) admitted to the ICU, 19 (33%) were intubated. Eight (7%) patients died.

Most cases were treated with a broad-spectrum cephalosporin (*n* = 104, 85%) and/or vancomycin (*n* = 55, 45%). Only 14 cases (11%) were treated with penicillin at any time during their illness, and no cases were treated exclusively with penicillin. Of the 14 cases that received penicillin, 3 were pediatric cases (ages 3 months, 3 months, and 17 years) and 11 were adults between the ages of 18 and 64. None of the penicillin recipients died. A comparison of characteristics between penicillin recipients and nonrecipients can be seen in Table 1.

Antimicrobial susceptibility testing results were available in the medical record for 30 of the 122 cases. The reported AST method used was disk diffusion in 9 cases (30%), Etest in 1 case (1%), broth microdilution in 1 case (1%), and unspecified in 19 cases (63%). The median interval from the date of first positive culture to the AST report date was 1 day (range, 0–24 days). Of the 30 cases with AST, 19 had AST for penicillin. Five of these 19 (26%) were treated with penicillin, both before and after AST results. Penicillin recipients were more likely to have AST than nonrecipients (*P* = .04) (Table 1). All 3 of the pediatric cases that received penicillin also had AST. The AST results reported in the medical records included 1 case each of penicillin resistance, penicillin intermediate susceptibility, ciprofloxacin resistance, and rifampin resistance and 3 cases of sulfamethoxazole/trimethoprim resistance. The testing method was disk diffusion in the case of rifampin resistance

Table 1. Characteristics of Cases of *Neisseria meningitidis*, Active Bacterial Core Surveillance, 2009

	Penicillin Given		<i>P</i> Value
	Yes (<i>n</i> = 14)	No (<i>n</i> = 108)	
Age in years, mean	31.1	32.3	.89
Age group, <i>n</i> (%)			
Pediatric	3 (21.4)	41 (38.0)	—
Adult	11 (78.6)	67 (62.0)	.38
Male, <i>n</i> (%)	10 (71.4)	48 (44.4)	.09
Syndrome, <i>n</i> (%)			
Bacteremia	3 (21.4)	33 (33.0)	—
Bacteremic pneumonia	0	18 (18.0)	.54
Meningitis	8 (57.4)	44 (44.0)	.51
Other	3 (21.4)	5 (5.0)	.06
AST performed, <i>n</i> (%)	7 (50.0)	23 (22.12)	.04
ICU admission, <i>n</i> (%)	8 (57.1)	49 (46.2)	.56
Intubation, <i>n</i> (%)	4 (30.8)	17 (19.3)	.46
ID consult, <i>n</i> (%)	13 (92.9)	71 (66.4)	.06
Died, <i>n</i> (%)	0	8 (7.4)	.59

The bold value indicates a statistically significant difference between penicillin recipients and non-recipients.

Abbreviations: AST, antimicrobial susceptibility testing; ICU, intensive care unit; ID, infectious diseases.

and the 3 cases of sulfamethoxazole/trimethoprim resistance. The testing method was unknown in the other cases of resistance and intermediate susceptibility.

Of the 123 cases reported to ABCs in 2009, 101 had AST performed at the CDC. Thirty-seven cases (37%) showed intermediate penicillin susceptibility, and 1 case showed penicillin resistance. Of these 37 intermediate penicillin-susceptible cases, 2 were treated with penicillin. All of the 101 isolates tested at the CDC were susceptible to ceftriaxone, ciprofloxacin, rifampin, and azithromycin.

The penicillin-resistant case identified in the medical record review did not have an isolate available for testing at the CDC. The case of intermediate penicillin susceptibility identified in the medical record was also identified as a case of intermediate penicillin susceptibility at the CDC. None of the cases of intermediate penicillin susceptibility or resistance identified at the CDC had AST results in their medical records. The case of ciprofloxacin resistance identified in the medical record review was tested at the CDC and was found to be susceptible to ciprofloxacin.

DISCUSSION

Our findings suggest that penicillin is not being used frequently to treat meningococcal disease with only 11% of cases in 2009 receiving penicillin in the ABCs sites. Antimicrobial susceptibility testing is not widely available, but it is noteworthy that AST was performed more frequently in penicillin recipients versus nonrecipients, and a variety of AST methods were used in the clinical laboratories. Our findings are consistent with results from a recent survey of infectious disease physicians on reported

practice for the management of meningococcal disease, which found that US physicians frequently continue treatment with third-generation cephalosporins rather than switching to penicillin after microbiological confirmation of *N meningitidis*, irrespective of the availability of AST [6]. The most common reasons for not switching included concerns about CSF penetration, a desire not to change working treatments, and the cost effectiveness and ease of use of cephalosporins. Some physicians did report continued treatment with cephalosporins as a result of concerns about antibiotic resistance or the lack of availability of AST.

Cases of invasive meningococcal disease caused by strains with reduced susceptibility to penicillin were first reported in the 1980s in United Kingdom, Spain, and South Africa but are now identified worldwide [7]. The first reported cases of disease caused by meningococci with reduced susceptibility to penicillin in the United States were in the early 1990s [7]. Studies evaluating whether meningococcal disease with reduced susceptibility to penicillin results in higher morbidity and mortality are inconclusive, but recent studies show no association with either intermediate penicillin susceptibility or penicillin resistance and death [7–9].

Although the sample size was small, most cases included in this expanded medical record review were treated with a broad-spectrum cephalosporin and/or vancomycin, and no cases were treated exclusively with penicillin. Information on antibiotic start and stop dates and administration times were missing or inconsistently documented, making it difficult to determine whether AST or microbiological diagnoses were influencing prescribing decisions. All available isolates from cases included in this review were tested at the CDC and were susceptible to ceftriaxone, ciprofloxacin, rifampin, and azithromycin. The low levels of resistance to nonpenicillin antibiotics and the use of broad-spectrum antibiotics in most of the cases would limit any potential impact of intermediate penicillin susceptibility on clinical outcomes. As a result of these findings and the relatively low levels of penicillin-reduced susceptibility, data were only collected for 2009, which may limit the relevance of the data because current practices may have changed.

CONCLUSIONS

In summary, in 2009 penicillin was not commonly used for treatment of meningococcal disease in the United States

There are likely several reasons for this, including inconsistent availability of AST, ease of use of third-generation cephalosporins, and reduced susceptibility to ceftriaxone being more rare than reduced susceptibility to penicillin. Consideration of current practices may inform future meningococcal disease management guidelines.

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